CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
IODINE

Chemical Code # 00718 Tolerance # 50404
SB 950 # 710
Original date: July 30, 2002

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, study inadequate, no adverse effects indicated.
Chronic toxicity, dog:	Data gap, study not submitted
Oncogenicity, rat:	Data gap, inadequate study
Oncogenicity, mouse:	Data gap, study not submitted
Reproduction, rat:	Data gap, inadequate studies, possible adverse effects
Teratology, rat:	Data gap, study inadequate, possible adverse effect indicated.
Teratology, rabbit:	Data gap, study inadequate, possible adverse effect indicated.
Gene mutation:	Data gap, study inadequate, possible adverse effect indicated.
Chromosome effects:	Data gap, study not submitted
DNA damage:	Data gap, inadequate study, possible adverse effect indicated
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T020730
Original by: J. Kishiyama and Gee, 7/30/02

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

50404 - 014 118187 Todhunter, J. A. and W. A. McCombie "Toxicological data and assessment of iodine with regard to chronic toxicity, oncogenicity, reproductive effects, teratogenicity, and mutagenicity: A supplemental response for California Notice 92-2." (SRS International Corp., Washington, D. C., for The Iodophors Joint Venture, IODOTOX-SB950, 8/12/92) The submission consists of 53 pages of review, a bibliography and copies of the citations. It contains an opening statement that there is adequate information on iodine as an antimicrobial, it is on the GRAS list, and there is human experience beyond SB950 mandated studies. The active ingredient in the iodophor antimicrobial pesticides is iodine. In compiling the review, the world literature from 1965 to 1992 was searched. Because of the antimicrobial and cytotoxic properties of iodine, genotoxicity data were not included (page 7). The role of iodine in thyroid function was reviewed. The RDA as a function of age was presented. Plasma levels from diet and other sources were tabulated as a function of age and sex of humans. The authors state that homeostatic mechanisms regulate the body burden of iodine and accumulation would occur only when these are overwhelmed (e.g., greater than 10X the RDA). Iodine has been used in a number of clinical products, such as cough suppressants, expectorants, and antiseptics. [Some of these uses are included in citations below.] The summary statement indicates that 200 - 3000 fold elevation for a short period appears to be without significant adverse effect. These levels of iodine would be much greater than due to exposure to antimicrobial agents as pesticides. In terms of exposure during use of products containing iodophors, the route would be primarily dermal. Several pages of calculations of potential dermal absorption were presented and compared with the normal plasma levels at the RDA. Acute oral toxicity was evaluated as mainly due to gastrointestinal irritation and its sequences. The iodophor retards absorption from the GI tract and decreases local irritation. Serum clearance and urinary excretion are unaffected by the iodophor. When applied to the skin, iodine can be an irritant, precluding long-term dermal studies. Exposure by inhalation was presented as not probable. From a review of subchronic/chronic studies in animals, the authors concluded the NOEL to be 0.39 mg/kg-day in the diet from a 19 month feeding study in rats (Record # 139773). Iodine levels have been reported to reach a steady state several months after repeated exposure. This effect was interpreted by the authors to indicate that subchronic and chronic exposures are similar. A deficiency in iodine appears to be more important in oncogenicity than an excess, and is secondary to alterations in endocrine function. No evidence of tumors at other sites was reported in any of the longer term studies in animals. Both an excess and a deficiency of iodine appear to affect reproduction adversely but not cause terata. A risk assessment was presented for iodine from disinfectants and compared with the RDA of 2.2 μg/kg, which was calculated to be 220,000 to 1,400,000 higher than their "worst case" and very much smaller than in iodine supplemented vitamin preparations. Iodinism from excess iodine intake produces similar signs in multiple species, including lacrimation, nasal discharge, coughing, alopecia, exophthalmos and hyperthermia, due to stimulation of the mucosal glands of the respiratory tract (page 44). These disappear after exposure is ceased (page 42). No worksheet. Supplemental information. (Gee, 7/25/02)

50404 - 010 120323 Todhunter, J. A. and W. A. McCombie "Toxicological data and assessment of iodine with regard to chronic toxicity, oncogenicity, reproductive effects, teratogenicity, and mutagenicity: A supplemental response for California Notice 92-2." (SRS International Corp., Washington, D. C., for Iodophors Joint Venture, 8/12/92) Selected pages of record 118187 in 50404 - 014. Not reviewed.

50404 - 014 [118187] Harvey, S. C. "Antiseptics and disinfectants; fungicides;

ectoparasiticides." (Chapter 41, published in *The Pharmacological Basis of Therapeutics*, 7th ed., 1985) The antiseptic uses and properties of iodine were reviewed. Tincture refers to preparations with higher concentrations of iodine (e.g. > 2%) while solutions are lower in concentration and, in some cases, less irritating. Iodophors are organic carrier molecules, which modify dispersibility and penetrance. No worksheet. (Gee, 7/25/02).

50404 - 014 [118187] Haynes, R. C. and F. Murad "Thyroid and antithyroid drugs." (Chapter 60, pages 1389 - 1411, in *The Pharmacological Basis of Therapeutics,* 7th ed., 1985) Review of thyroid hormones, iodine metabolism and therapy. No worksheet. (Gee, 7/25/02)

CHRONIC TOXICITY, RAT

50404 - 042 139773 Tanaami, S., S. Katamine, N. Hoshino, K. Totsuka, and M. Suzuki. "Histopathological Study on Rats Fed Iodine-Enriched Eggs Long Term (7 and 19 Months)." (Research center, Nihon Nosan Kogyo K.K., Japan, published in *J. Nutrition Science and Vitaminology* 31: 29-42. (1985)) A long-term (7 and 19 months) feeding study with an iodine-enriched egg powder diet containing 392 μg iodine/100g of diet was compared with an ordinary egg powder diet (35 μg/100g of diet). Eight Sprague-Dawley male rats were sacrificed at 7 months and 11 males at 19 months. No significant treatment- related effects were reported. UNACCEPTABLE (major variances including no hematology, clinical chemistry, urinalysis or ophthalmology, single dose level, males only, inadequate number per group, others). Not upgradeable. (Kishiyama and Gee, 7/11/02).

Subchronic, rat:

50404 - 042 139771 Sherer, T. T., K. D. Thrall and R. J. Bull. "Comparison of Toxicity Induced by Iodine and Iodide in Male and Female Rats." (Washington State University, College of Pharmacy, published in *J. of Toxicology and Environ. Health*, 32: 89-101 (1991)). Iodine (I_2) and iodide (as NaI) (no purity given) were added to drinking water at concentrations of 1, 3, 10 or 100 mg/l and given to 6 Sprague-Dawley rats/sex/group for 100 days. The control group consisted of 12 rats/sex. Rats were housed 3/cage. Thyroid weight was increased in males and decreased in females with iodide. High doses of iodine increased the ratio of thyroid hormones (T_4/T_3) for males and females after 10 and 100 days of exposure, due primarily to a decrease in T_3. No histopathological findings in the thyroid. No other treatment related effects were reported. UNACCEPTABLE and not upgradeable (no ophthalmology, inadequate description of the test articles, limited clinical chemistry and hematology, limited histopathology.) Not upgradeable. Supplemental information. (Kishiyama and Gee, 7/11/02).

CHRONIC TOXICITY, DOG

Study not submitted

ONCOGENICITY, RAT

50404 - 042 139786 Ohshima, M and J. M. Ward. "Promotion of N-Methyl-N-Nitrosourea-Induced Thyroid Tumors by Iodine Deficiency in F344/NCr Rats." (National Institutes of Health, Cancer Research Facility, published in the *J. Natl. Cancer Inst.* 73 (1): 289 - 296 (1984)). Male

F344/NCr rats (20/group), injected once with 41.2 mg of N-Methyl-N-Nitrosourea (MNU)/kg BW at week 6 of age, were fed, beginning week 8, for up to 31 weeks with either iodine-deficient (ID), iodine adequate (IA with 0.01 g potassium iodate per kg b.wt.) or WLB control diet. Sacrifices were performed after 18 or 31 weeks on selected diets, with 10 per group per time. MNU-injected rats plus any one of three diets had a significant increase in thyroid follicular lesions, focal alveolar type II lung cell hyperplasia and retinal atrophy. Body weight was also reduced compared with sodium citrate controls. MNU-injected rats fed ID diet appeared more prone to effects on the thyroid and body weight than those fed IA diet, especially for diffuse follicular hyperplasia and follicular carcinomas. At 20 weeks, MNU + ID diet rats already had significant incidences of diffuse follicular hyperplasia and adenomas. Mean number of focal proliferative follicular lesions was also increased at 20 weeks versus other groups. Follicular adenomas were increased at 10/10, 7/10 and 5/10 in MNU-treated groups on ID, IA and WLB diets at 33 weeks. Iodine-deficient diet alone also increased diffuse follicular hyperplasia 10/10 versus 0/10 in IA and WLB groups. The ID diet appeared to be a promoter of MNU initiated thyroid tumors but had no affect on other organs. UNACCEPTABLE (many deficiencies including length of treatment, number and sex of animals, missing histopathology, others). Not upgradeable/supplemental information. (Kishiyama and Gee, 7/12/02).

ONCOGENICITY, MOUSE

Study not submitted

REPRODUCTION

50404 - 042 139787 Arrington, L. R., R. N. Taylor Jr., C. B. Ammerman, and R. L. Shirley. "Effects of Excess Dietary Iodine upon Rabbits, Hamsters, Rats, and Swine." (Department of Animal Science, University of Florida, published in *Journal of Nutrition*. 87: 394 - 398 (1965)) Potassium or sodium iodide was mixed with the feed during selected life phases at concentrations of iodine of 0, 250, 500 or 1000 ppm for rabbits, 2500 ppm for hamsters (12 days) and rats and at 1500 and 2500 ppm for swine. Rat and rabbit pup survival and weights were reduced when dams were fed before parturition. At 2500 ppm, rat gestation time was normal but parturition time was extended. Hamster pup weight was reduced at 21 days. When rats and rabbits that had lost their litters were taken off iodine and mated, reproduction was normal. There were no effects reported for swine fed KI for 30 days before farrowing. At 2500 ppm, doses in mg/kg were approximately 160 for hamsters, 150 for rats, 90 for rabbits and 41 for swine. Possible adverse effects on early pup survival in rabbits and rats. UNACCEPTABLE, not upgradeable. (Major variances and insufficient information). (Kishiyama and Gee, 7/15/02).

50404 - 042 139789 Wilson, H. R. and L. O. Rowland, Jr. "High dietary iodine and reproduction in the cock." (University of Florida, abstract, *J. Reprod. Fertil.* 18: 181 (1969)) Potassium iodide was fed to 25 week old and 40 week old male Single-Comb White Leghorn chickens at 5000 ppm for 8 weeks. One group was held for a 1-week recovery period. The effect on semen volume, sperm concentration, percentage of dead spermatozoa, fertility and hatchability were determined periodically. The percentage of dead spermatozoa increased the first week of iodine exposure and remained high while on iodine. Iodine reduced fertility but had little effect on hatchability. Birds showed signs of iodinism with difficulty standing and moving in a coordinated manner, especially when excited. These signs began disappearing the 3rd and 4th day

after feeding iodine was stopped. No worksheet. (Gee, 7/15/02).

50404 - 042 139790 Jones, R. E., R. J. Aulerich, and R. K. Ringer. "Feeding Supplemental Iodine to Mink: Reproductive and Histopathological Effects." (published in *J. Toxicol. Environ. Health* 10: 459 - 471 (1982)). Potassium iodide was fed as a supplement at concentrations of 0, 10, 20, 40, 80 or 160 ppm iodine (7 months, long term) and at 40, 80, 160, 320 ppm iodine (1 month, short term) added to the basal diet and fed to 12 female and 3 male mink/group prior to breeding. Sperm appeared normal. Gestation length was not affected**.** Iodine content of milk was proportional to the diet. Thyroid glands of kits showed marked hyperplasia at > 20 ppm with hyperplastic follicular cells and decreased amount of colloid. Adult thyroids at > 40 ppm also showed mild hyperplasia of follicular cells and decrease in lumen size and colloid content. Gallbladders of adults showed pathological lesions related to dose at 80 ppm and above. **Iodine supplements at 160 ppm and higher caused inferior reproduction for mink, e.g., lower kit survival, smaller live litter size, lower body weight at birth and week 4.** UNACCEPTABLE (major variances and insufficient information). (Kishiyama and Gee, 7/15/02)

TERATOLOGY, RAT

50404 - 042 139787 Arrington, L. R., R. N. Taylor Jr., C. B. Ammerman, and R. L. Shirley. "Effects of Excess Dietary Iodine upon Rabbits, Hamsters, Rats, and Swine." (Department of Animal Science, University of Florida, published in *Journal of Nutrition*. 87: 394 - 398 (1965)) Potassium or sodium iodide was mixed with the feed during selected life phases at concentrations of iodine of 0, 250, 500 or 1000 ppm for rabbits, 2500 ppm for hamsters (12 days) and rats and at 1500 and 2500 ppm for swine. Rat and rabbit pup survival and weights were reduced when dams were fed before parturition. At 2500 ppm, rat gestation time was normal but parturition time was extended. Hamster pup weight was reduced at 21 days. When rats and rabbits that had lost their litters were taken off iodine and mated, reproduction was normal. There were no effects reported for swine fed KI for 30 days before farrowing. At 2500 ppm, doses in mg/kg were approximately 160 for hamsters, 150 for rats, 90 for rabbits and 41 for swine. Possible adverse effects on early pup survival in rabbits and rats. UNACCEPTABLE, not upgradeable. (Major variances and insufficient information). (Kishiyama and Gee, 7/15/02).

TERATOLOGY, RABBIT

50404 - 042 139787 Arrington, L. R., R. N. Taylor Jr., C. B. Ammerman, and R. L. Shirley. "Effects of Excess Dietary Iodine upon Rabbits, Hamsters, Rats, and Swine." (Department of Animal Science, University of Florida, published in *Journal of Nutrition*. 87: 394 - 398 (1965)) Potassium or sodium iodide was mixed with the feed during selected life phases at concentrations of iodine of 0, 250, 500 or 1000 ppm for rabbits, 2500 ppm for hamsters (12 days) and rats and at 1500 and 2500 ppm for swine. Rat and rabbit pup survival and weights were reduced when dams were fed before parturition. At 2500 ppm, rat gestation time was normal but parturition time was extended. Hamster pup weight was reduced at 21 days. When rats and rabbits that had lost their litters were taken off iodine and mated, reproduction was normal. There were no effects reported for swine fed KI for 30 days before farrowing. At 2500 ppm, doses in mg/kg were approximately 160 for hamsters, 150 for rats, 90 for rabbits and 41 for swine. Possible adverse effects on early pup survival in rabbits and rats. UNACCEPTABLE, not upgradeable. (Major variances and insufficient information). (Kishiyama and Gee, 7/15/02).

GENE MUTATION

50404 - 042 139793 Kessler, F. K., D. L. Laskin, J. F. Borzelleca and R. A. Carchman. "Assessment of Somatogenotoxicity of Povidone-Iodine Using Two *In Vitro* Assays". (Medical College of Virginia, published in *J. Environ. Pathol. Toxicol.* 4-2,3:327 - 335 (1980)) Povidone-iodine (PVP-I) and polyvinyl pyrolidone (PVP), both with and without metabolic activation, were assayed at concentrations of 0, 100 and 500 μg/ml and 1, 5, 10 mg/ml and at 0, 1, 5, 10, 50, and 100 mg/ml, respectively, for mutagenic potential using mouse lymphoma L5178Y cells. Potassium iodide (500 μg to 10 mg/ml) and iodine (22-340 μg/ml) without S9 Mix were also included. Incubation was for 4 hours followed by an expression period. Six replicate plates were made for mutant frequency. No viability data were provided. **PVP-I (5 mg/ml with S9 Mix) gave a statistically significant increase in mutant frequency (4.74 versus 1.0)**, but not at 10 mg/ml (only 8% survival by dye exclusion). For cell transformation, BALB/c3T3 cells were exposed to the same concentrations for 48 hours, followed by 21 days for foci formation using 18 replicate plates. A **statistically significant increase in the number of foci** was seen with iodine at 170 μg/ml and with PVP-I at 5 mg/ml, without a dose relationship at higher or lower concentrations. Positive controls were functional. The authors considered these results as biologically not significant. Summary data only. UNACCEPTABLE (insufficient information for an independent evaluation). (Kishiyama and Gee, 7/15/02).

CHROMOSOME EFFECTS

Study not submitted

DNA DAMAGE

50404 - 042 139793 Kessler, F. K., D. L. Laskin, J. F. Borzelleca and R. A. Carchman. "Assessment of Somatogenotoxicity of Povidone-Iodine Using Two *In Vitro* Assays". (Medical College of Virginia, published in *J. Environ. Pathol. Toxicol.* 4-2,3:327 - 335 (1980)) Povidone-iodine (PVP-I) and polyvinyl pyrolidone (PVP), both with and without metabolic activation, were assayed at concentrations of 0, 100 and 500 μg/ml and 1, 5, 10 mg/ml and at 0, 1, 5, 10, 50, and 100 mg/ml, respectively, for mutagenic potential using mouse lymphoma L5178Y cells. Potassium iodide (500 μg to 10 mg/ml) and iodine (22-340 μg/ml) without S9 Mix were also included. Incubation was for 4 hours followed by an expression period. Six replicate plates were made for mutant frequency. No viability data were provided. **PVP-I (5 mg/ml with S9 Mix) gave a statistically significant increase in mutant frequency (4.74 versus 1.0)**, but not at 10 mg/ml (only 8% survival by dye exclusion). For cell transformation, BALB/c3T3 cells were exposed to the same concentrations for 48 hours, followed by 21 days for foci formation using 18 replicate plates. A **statistically significant increase in the number of foci** was seen with iodine at 170 μg/ml and with PVP-I at 5 mg/ml, without a dose relationship at higher or lower concentrations. Positive controls were functional. The authors considered these results as biologically not significant. Summary data only. UNACCEPTABLE (insufficient information for an independent evaluation). (Kishiyama and Gee, 7/15/02).

MISCELLANEOUS

50404 - 042 139770 Allen, E. M., M. C. Appel, and L.E. Braverman . "Iodine-Induced Thyroiditis and Hypothyroidism in the Hemithyroidectomized BB/W Rat." (Division of Endocrinology and Metabolism and Department of Pathology, University of Massachusetts Medical School, Study Number IODO-RRP4-005, published in *Endocrinology* 121**:** 481-485 (1987)). Iodine (form unclear) was administered in the drinking water at a concentration of 0.05% I for 60 - 69 days to 14 to 39 female rats per strain (Biobreeding Worcester (BB/W), W-line, Wistar-Furth and Sprague-Dawley). Hemithyroidectomized (day 30 of age) BB/W and W-line rats had reduced body weight with iodine. Lymphocytic thyroiditis (LT) was induced only for BB/W rats. BB/W and W-line rat strains had increased concentrations of antithyroglobulin antibodies (Anti-Tg), and TSH . T3 and T4 were decreased or the same. Thyroid weight was increased in BB/W and W-line rats, associated with lymphocytic thyroiditis.. Results indicated a possible genetic relationship for iodine-induced hypothyroidism. Thyroid function was unaffected for hemithyroidectomized Wistar and Sprague Dawley rat strains. Supplemental information. (Kishiyama and Gee, 7/11/02)

50404 - 042 139765 Fakouhi, T. A.. C. Griffin, R. S. McCutcheon, and J. F. Bone. "Toxicology of the Iodophor, Imidecyl Iodine." (Department of Veterinary Medicine, Oregon State University, Study No. IODO-RRP4-001, published in *Journal of Pharmaceutical Sciences*, **56**, No.9, 1186 - 1188 (September, 1967.) Imidecyl iodine (amphodyne, iodine content not reported) was evaluated for toxicological properties with various species and different routes of administration. LD_{50} (rats) = 14.0 "2.1 ml/Kg for males and 11.0 "1.5 ml/Kg for females. There were no deaths at 4 ml/kg. Microscopic lesions included pulmonary edema, ascites, distended stomach, hyperemia and damage to the liver and kidneys. Imidecyl iodine undiluted in acute dermal (rat), guinea pig sensitization and rabbit eye toxicity studies caused no significant reaction. Instillation of 15 ml at various dilutions into the empty urinary bladder of rabbits for 30 minutes caused death/irritation up to 1:64 dilution. A dilution of 1:128 caused no visible lesions. A 1:15 dilution in a subchronic toxicity caused no adverse effects when given orally to three male dogs 4 times weekly over 90 days to 5 months. All studies UNACCEPTABLE (major variances and insufficient information including no verification of doses). (Kishiyama and Gee, 7/10/02).

50404 - 042 139766 Glick, P. L., B. J. Guglielmo, R. F. Tranbaugh and K. Turley "Iodine toxicity in a patient treated by continuous Povidone-iodine mediastinal irrigation." (Published in *The Annals of Thoracic Surgery* 39 (5): 478 - 480 (1985)) A 34-month old male was subjected to continuous mediastinal irrigation with a 5% solution of povidone-iodine (Betadine) following surgery. Two days later, metabolic acidosis developed associated with lethargy and agitation. Serum iodine was 9,375 μg/dl (normal range, 4.5 to 9 μg/dl). The concentration was reduced to 1.%, then to 0.5%. The patient developed cardiac insufficiency and died on the 6th day. The discussion section stated that signs and symptoms of iodine toxicity are "…nonspecific, anecdotal and sporadic." The conclusion was that mediastinal irrigation with povidone-iodine is contraindicated. No worksheet. Supplemental information. (Gee, 7/10/02)

50404 - 042 139768 Caille, J. M. and M. Allard "Neurotoxicity of hydrosoluble iodine contrast media." (Published in *Invest. Radiol.* 23 (suppl 1): S210 - S212 (1988)) Ionic monomers, monoacid ionic dimers (ioxaglate) and nonionic monomers (iopamidol, iohexol) and dimers (iotrol, iotrolan) were discussed. Neurotoxicity was stated as a function of osmolarity, presence of sodium ion and lipid solubility. Also, whether the blood-brain barrier is intact, the clearance time, the patient and the injection site (intravascular, intrathecal) are additional factors. No worksheet. Supplemental information. (Gee, 7/10/02).

50404 - 042 139769 Hillman, D. and A. R. Curtis "Chronic iodine toxicity in dairy cattle: Blood chemistry, leukocytes and milk iodine." (Published in *J. Dairy Sci,.* 63: 55 - 63 (1980)) Holstein cows received either normal (16 mg per day, range of 11 to 25) or high iodide (164 mg per day, range of 74 to 402) in the feed. Excess iodide was given as ethylenediamine dihydriodide (EDDI). The amount supplied by the diet from hay, silage and water were considered equal for the two groups. Cows were in early (<90 days), middle (90 to 120 days) or late (>120 days) lactation. Blood and serum were analyzed for hemoglobin, hematocrit and cell counts including differential leukocytes. Serum was analyzed for thyroid stimulating hormone (TSH) and thyroxine (T4). Iodide content of urine and milk was determined. Milk iodide averaged 0.37 ppm for normal cows and 2.16 ppm for high iodide group. Milk iodide correlated with urinary iodide. Total leukocytes were similar for both groups but there was a shift in the types of leukocytes at high iodide with an increase in neutrophils (33% versus 43%) and a decrease in lymphocytes (57% versus 49%). There was also a slight decrease in eosinophils. Glucose concentration increased (48 versus 62 mg/dl), cholesterol decreased (170 versus 145 mg/dl), SGOT increased (55.7 versus 83.9 units/dl), but thyroxine and TSH were approximately the same. Thirteen cows were fed 19g thyroprotein for 2 weeks and 10g for one week. Results were compared with pretreatment values. Results were similar to those with EDDI. High iodide cows displayed signs of iodide toxicity including lacrimation, conjunctivitis, loss of hair around the eyes, coryza, dermatitis, and exophthalmus. The authors suggest that dietary iodide be limited with cattle. No worksheet. Supplemental information. (Gee, 7/10/02).

50404 - 042 139774 Newton, G. L. and A. J. Clawson "Iodine toxicity: Physiological effects of elevated dietary iodine on pigs." (North Carolina State University, published in *J. Animal Science* 39: 879 - 884 (1974)) There were three trials using calcium iodate as the source of iodine. The dietary requirement for swine was stated to be 0.2 ppm. Trial 1: Groups of 12 pigs (sex not stated) were fed diets containing added iodine at 0, 10, 20, 40 or 80 ppm for 84 days. Serum samples were taken at days 7, 28, 56 and 84 for iodine determination. Thyroids were weighed and liver was analyzed for iron content. There was no effect on body weight or food intake. Serum iodine levels increased with dose (9.32 μg/100 ml in control and 293.5 μg/100 ml at 80 ppm. Thyroid weight also increase with increasing dose, being statistically significant at all added iodine doses. There was no effect on liver iron. Trial 2: Seven or eight pigs were fed diets with added iodine at 0, 25, 50, 100, 200, 400, 800 or 1600 ppm for up to 111 days. Serum samples were taken at days 14, 42, 70 and 97 days with blood taken at 104 and 111 days for hemoglobin. Four per group were slaughtered on day 97 and four on day 111. Thyroids were weighed and liver analyzed for iron. Body weight gain and food intakes were significantly lower at 800 and 1600 ppm. Hemoglobin (g/100 ml) was lower at 800 and 1600 ppm, serum iodine increased with dose and liver iron was significantly lower at 400 ppm and above. Thyroid weight also increased with dose (82.0 mg/kg body weight in controls and 237.0 mg/kg at 1600 ppm. Trial 3: Six pigs were fed diets with 0, 800, 800 iodine plus 2140 ppm added iron (ferrous sulfate) or 800 plus 75 mg/pig/week iron as iron dextran by im injection for 70 days. Blood samples were taken at 0, 14, 28, 42, 56 and 70 days for hemoglobin determination. Pigs in the control group gained faster than those receiving iodine but no iron. Pigs receiving iodine plus iron were intermediate. Thyroid weights were not affected by the addition of iron, being increased about the same as 800 ppm iodine with no added iron. The authors concluded that the minimum toxic level of iodine from calcium iodate was between 400 and 800 ppm. Considering iron levels in liver, the minimum toxic level for an extended period may be below 400 ppm. No worksheet. Supplemental information. (Gee, 7/11/02).

50404 - 042 139776 Newton, G. L., E. R. Barrick, R. W. Harvey and M. B. Wise. "Iodine toxicity Physiological effects of elevated dietary iodine on calves." (North Carolina State

University, published in *J. Animal Science* 38: 449 - 455 (1974)). Iodine as calcium iodate was added to diets of Holstein bull calves beginning about age 10 to 14 weeks. Iodine requirement was given as 0.1 ppm in the diet. Trial 1: Eight calves per group were fed diets with added iodine at 0, 10, 100 or 200 ppm for 104 days. Blood samples were taken approximately every 14 days for hemoglobin, serum calcium and iodine. Thyroid glands and rumen fluid were obtained at termination. Feed intake and body weight gain were lower at 100 and 200 ppm. Thyroid weight was increased at 200 ppm. Serum iodine was increased with increasing dose while serum calcium was significantly lower at 200 ppm. Hemoglobin was lower at 100 and 200 ppm. Calves fed at 100 and 200 ppm developed chronic coughs within 14 days and had profuse nasal discharge. At 200 ppm, these effects persisted while at 100 ppm, the discharge diminished with time. Trial 2: Eight calves per group were fed diets with added iodine at 0, 25, 50 or 100 ppm for 112 days. Thyroid and adrenal glands were collected at termination and blood was drawn periodically. Food intake and body weight gain were lower at 100 ppm compared with controls. Thyroid and adrenal weights were increased at all doses. Serum calcium levels were comparable at all doses while serum iodine increased with increasing dose. Although less marked than in trial 1, calves developed coughing and nasal discharge at 25 (5/8), 50 (6/8) and 100 (6/8) ppm. Trial 3: Eight calves per group were fed 0, 10, 25 or 50 ppm added iodine for 111 days. Thyroid and adrenal glands were collected at termination. Blood samples were taken periodically for hemoglobin analysis. Calves at 50 ppm gained less weight and consumed less feed. Thyroid weights were lower in the treated groups for unexplained reasons. Adrenal weights, however, were higher. Hemoglobin levels were not affected but serum iodine increased with dose. Coughing and nasal discharge developed in 7/8 at 50 ppm, 2/8 at 25 ppm and 1/8 at 10 ppm in the diet, being "very persistent and severe" in 2 at 50 and 1 at 25 ppm. The authors state that the effects were not uniform with dose with 1 calf at 25 ppm showing rather severe iodinism. The authors concluded that 25 ppm in the diet was too high and some calves at 10 ppm showed mild iodinism. No worksheet. Supplemental information. (Gee, 7/11/02)

50404 - 042 139777 McCauley, E. H., J. G. Linn and R. D. Goodrich "Experimentally induced iodide toxicosis in lambs." (Univ. of Minn., published in *Am. J. Vet. Res.* 34: 65 - 70 (1973)) Most groups consisted to 2/sex. Iodine was given as either ethylenediamine dihydroiodide (EDDI) or potassium iodide in gelatin capsules. Doses of EDDI were 94, 188, 375, 562 or 750 mg/day and KI, 196, 393, 589 or 785 mg/day. Dosing lasted 22 days followed by an observation period until day 31. The amounts of iodine from the two sources were calculated to be equivalent (except for the 94 mg/day group). Blood samples were collected and rectal temperatures recorded during the dosing period. Serum protein bound iodine was determined. RESULTS: At higher doses of iodine, clinical observations of central nervous system depression and coughing and anorexia occurred. Food intake and weight gain were lower at higher doses and did not return to control levels during the 7-day postdosing period. Hyperthermia was seen in all treated groups. Total serum iodine and protein bound iodine were increased with dose and persisted during the 7-day post-treatment period. Four lambs at higher doses died of bronchopneumonia. The authors discussed the relationship of iodine to possible causes of these deaths (inflammatory response mechanism) and to hyperthermia (increase in metabolic rate by uncoupling oxidative phosphorylation). Supplemental information. No worksheet. (Gee, 7/12/02).

50404 - 042 139779 Haggard, D. L., H. D. Stowe, G. H. Conner and D. W. Johnson "Immunologic effects of experimental iodine toxicosis in young cattle." (Michigan State University, Published in *Am. J. Vet. Res.* 41 (4): 539 - 543 (1980)) Iodine as ethylenediamine dihydroiodide was given orally in an aqueous vehicle to 10 Holstein-Fresian heifer calves for 6 months. Doses were 0, 50, 250 or 1250 mg of iodine per day. Average weight was120 kg.

Humoral and cell-mediated immune responses were measured using antibody responses to a live bacterial antigen (strain 19 brucella vaccine), a killed bacterial antigen (leptospira bacterin), a modified live virus (infectious bovine rhinotracheitis (IBR)), lymphocyte mitoses stimulated by phytohemagglutin, pokeweed and conconavalin A in vitro for [^{3}H]thymidine uptake, intradermal PHA response, phagocytosis of *Candida albicans* by WBC and total WBC counts. More changes in immune response were seen at the high dose of iodine than at the lower doses. The results in calves indicated that excessive iodine for extended periods may cause antibody titer for some antigens to decline, decreased mitotic activity of lymphocytes, decreased phagocytic activity and lower WBC counts. The authors concluded the results indicate impaired humoral and cell-mediated immune systems. No worksheet. Supplemental information (many missing parameters). (Gee, 7/12/02).

50404 - 042 139780 Fish, R. E. and E. W. Swanson "Effects of excessive intakes of iodine upon growth and thyroid function of growing Holstein heifers." (University of Tennessee, published in *J. Dairy Sci.* 65: 605 - 610 (1982)) Groups of six Holstein heifers were given doses of iodine at 0 (<1ppm I), 0.625, 1.25, 2.5 or 5.0 mg I/kg body weight as ethylenediamine dihydroiodide (EDDI) in feed for 12 weeks. Blood was collected at weeks 0, 4, 8 and 12 for determination of iodine, thyroxine (T_4) and triiodothyronine (T_3) in plasma. Iodine increased with dose, peaking at week 8 sampling. Serum levels of T_3 and T_4 were generally comparable although there was a minor alteration in thyroid function at 5.0 mg/kg b. wt. Signs of iodinism were nasal discharge, lacrimation and moderate coughing, apparently in all groups (no details). Weight gain was lower at 5 mg/kg early in the study. No worksheet. Supplemental information. (Gee, 7/12/02).

50404 - 042 139782 Martino, E., F. Aghini-Lombardi, S. Mariotti, L. Bartalena, L. Braverman and A. Pinchera "Amiodarone: A common source of iodine-induced thyrotoxicosis [human data]." (Published in *Hormone Research* 26: 158 - 171 (1987)) Amiodarone contains 37.2 mg iodine/100 mg compound and is used to treat ischemic heart disease and tachyarrhythmias. A group of patients (32 males, 24 females) with amiodarone-iodine-induced thyrotoxicosis (AIIT) living in a mild iodine-deficient area of Italy were studied. All patients had received chronic treatment (range 4 - 73 months) at doses of 0.6 to 2.8 g/week for tachyarrhythmias. Serum Total T_4, total T_3, free T_4, free T_3, reverse T_3 (rT_3), thyroglobulin, and TSH were assayed. Thyroid radioiodine uptake was determined 24 hours after exposure to ^{131}I. 84% of the cases occurred during treatment and 16% at 1 - 11 months after drug withdrawal (amiodarone has a long half-life and can bioaccumulate). Diffuse goiter was present in 17 patients, uni-or multinodular goiter in 38% and normal thyroids in 33%. The measured parameters were elevated in nearly all patients with AIIT. Urinary iodine excretion was markedly elevated Serum TSH was undetectable. The 24-hour thyroid uptake of radioiodine was very low or undetectable in AIIT patients with apparently normal thyroids and inappropriately elevated with underlying thyroid disorders. Therapy for AIIT was discussed. No worksheet. Supplemental information. (Gee, 7/12/02).

50404 - 042 139784 Belfiore, A., L. Sava, F. Runello, L. Tamaselli and R. Vigneri "Solitary autonomously functioning thyroid nodules and iodine deficiency." (Published in *J. of Clinical Endocrinology and Metabolism* 56 (2): 283 - 287 (1983)) The incidence of autonomously functioning thyroid nodules (AFTN) was evaluated in 31,373 patients from two sections of Sicily between 1965 and 1980. The incidence in an iodine-sufficient area of Sicily was 2.7% and in iodine-deficient area, 4.4%. Diagnosis included presence of a single thyroid nodule that concentrated ^{131}I to a greater degree than surrounding thyroid tissue. Iodine deficiency was suggested as a factor in the development of AFTN. No worksheet. Supplemental information. (Gee, 7/12/02).

50404 - 042 139785 Clayson, D. "Nutrition and experimental carcinogenesis: a review." (University of Nebraska Medical Center, published in *Cancer Research* 35: 3292 - 3330 (1975)) Iodine was one of the dietary factors discussed. Iodine deficiency or goitrogens may lead to tumors. No worksheet. Supplemental information. (Gee, 7/12/02)

50404 - 042 139794 Glick, P. L., B. J. Guglielmo, M. E. Winter, W. Finkbeiner and K. Turley "Iodine toxicity secondary to continuous povidone-iodine mediastinal irrigation in dogs." (Published in *J. Surgical Res.* 49: 428 - 434 (1990)) Three mongrel dogs were irrigated with 0.5% povidone-iodine for up to 48 hours via catheters. Iodine absorption was measured by determining serum and urine levels as a function of time. Tissue samples of the heart, pericardium, liver and kidney were examined histologically. Iodine at steady-state was 29,290 μg/dl. T1/2 was 6.22 hours. The pericardium and heart showed marked acute inflammation and fat necrosis of the epicardial adipose tissue. Kidneys and liver were normal. Absorption of iodine was considered similar to iv injection. No worksheet. Supplemental information. (Gee, 7/15/02)

50404 - 041 139795 Hunt, J. L., R. Sato, E. L. Heck and C. R. Baxter "A critical evaluation of povidone-iodine absorption in thermally injured patients." (Published in *J. Trauma* 20 (2): 127 - 129 (1980)) Seventeen patients were treated within 24 hours of injury with an ointment containing 10% povidone-iodine with 1% available iodine. Burns covered 8 to 85% of the body. Ointment was applied every 12 hours up to 7 days. Serum and urinary iodine were measured. Thyroid function was not affected. The highest serum iodine levels were in patients with renal failure. Normal range of iodine in serum was given as 0 - 3 μg/dl. Peak levels in patients ranged from 595 to 4900 μg/dl and remained elevated for as long as 7 days after cessation of therapy and was related to renal function. No worksheet. Supplemental information. (Gee, 7/15/02)

50404 - 041 139796 Feldmann, R. J. and H. I. Maibach "Absorption of some organic compounds through the skin in man." (Published in *J. Investigative Dermatol.* 54: 399 - 404 (1970)) Twenty-one compounds were studied for absorption through the skin of the forearm by measuring excretion in the urine. Iodine per se was not one of them. No review. No worksheet. (Gee, 7/15/02).

50404 - 042 139797 Feldmann, R. J. and H. I. Maibach "Percutaneous penetration of some pesticides and herbicides in man." (Published in *Toxicol. Appl. Pharmacol.* 28: 126 - 132 (1974)) Twelve radiolabeled compounds were tested on the forearm of human male subjects and excretion of ^{14}C in urine measured over 5 days. Doses of 4 $\mu g/cm^2$ dissolved in acetone were used. Data from iv injection was used to correct urinary recovery. The least absorbed was diquat and the most absorbed was carbaryl. Iodine was not among the active ingredients. Supplemental information. No worksheet. (Gee, 7/16/020